REMARKS

By this amendment, claims 25 and 27-34 are pending. Claim 25 is amended. Claims 25 and 27-34 are believed consonant with elected Group I of the Restriction Requirement as drawn to a method for identifying compounds that bind to a target of interest. No new matter is added by the amendments.

The Applicant thanks the Examiner for the courtesy of a telephone interview on 16 May 2006.

Rejection under 35 USC § 112, second paragraph

Claims 25 and 27-34 stand rejected under 35 USC § 112, second paragraph as allegedly indefinite. Claim 25, from which all claims depend, is alleged vague and indefinite because two clauses are unclear.

The first clause, "wherein the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups" is believed clear on its face. The term "functional group" is well known in the art as applied to a molecule such as the ligands described in claim 25. The functional groups include those described by properties in the clause preceding the allegedly vague and indefinite clause. As to the functional groups which bind to the target biomolecule or provide for linking between the first and second ligands, the applicant is not to be construed. Exemplary functional groups are described in the specification, for example at page 25, lines 6-10.

The second clause, "whereby the compound that binds to the target is identified" is amended by insertion of: "linked ligand" to make clear that it is the linked ligand compound that binds to the target which is identified.

Rejection under 35 USC § 103(a)

Claims 25, 28, 30, 31, 34 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Griffey in view of Hajduk et al, J. Am. Chem. Soc. 1997, 119, 5818-5827, ("Hajduk").

The rejection is respectfully traversed. To establish *prima facie* obviousness, all the claim limitations must be taught or suggested by the cited art (MPEP 2143.03). Claim 25 includes: (i) the step of identifying a 1:1 complex of linked ligand and target

biomolecule by detecting the non-covalent binding of the linked ligand compound to the target biomolecule by mass spectrometry; (ii) members of the first and second set of ligands to having one or more functional groups selected from hydrogen bond donors, hydrogen bond acceptors, functional groups which form a cation at physiological pH, functional groups which form an anion at physiological pH, and functional groups which form hydrophobic interactions; and (iii) the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups.

Applicant disagrees that Griffey teaches element (i). Column 24 of Griffey, cited by the Examiner as evidence that Griffey teaches element (i), merely discloses that new concatenated ligands may be screened and affinities measured for their binding to target, in the same manner as were the parent ligands. Griffey does not teach identifying a 1:1 complex of parent ligand binding to target. Element (i) requires a 1:1 complex of linked ligand compound and target biomolecule, an aspect disclosed and enabled in the present application, but not in Griffey. Support for methods of identifying a 1:1 complex may be found, among other places in the specification, at page 1, line 12; page 10, lines 16-17; page 15, lines 11-14; page 16, line 26; page 19, lines 16-18; and in particular, at page 21, lines 25-27; at page 45, lines 16-21; and at page 47, lines 6-9 and 17-20. Griffey does not teach a 1:1 complex, or a complex where one linked ligand compound is non-covalently bound to a target biomolecule. Griffey does not teach the value of screening for 1:1 complexes, which the present invention has discovered. Griffey teaches forming complexes "with the target with an affinity greater than baseline". The value or utility of establishing a baseline affinity is not disclosed in Griffey, nor does Griffey disclose how to establish a baseline affinity and what the person skilled in the art should do with it.

In contrast, the present invention teaches that optimizing linked ligand binding to target biomolecule includes selecting those which form a 1:1 ratio, i.e. where a single linked ligand molecule binds to a single target molecule. The present invention also teaches how to detect and measure 1:1 complexes. A 2:1 complex of linked ligand and target biomolecule is taught by the present invention to not be optimal. See page 25, lines 22-25.

Neither Griffey nor Hajduk teach or suggest any one of elements (i), (ii) or (iii). The cited references thus collectively fail to teach or suggest all the elements of the claimed subject material.

For reasons stated in Applicant's reply of 9 January 2006 and herein, Applicant asserts that Griffey is defective as a prior art reference for the purposes of: (a) enabling that the target molecule can be proteins; (b) teaching ligands with the functional groups of present claim 25; or (c) teaching ligands that have different functional groups.

"Concatenating", a key term in Griffey, is vague and indefinite. Griffey does not teach how to concatenate ligands. Griffey speaks only conceptually and prophetically about "ligand fragments that are concatenated together in a structural configuration that improves the binding properties of the fragments for the invention (column 5, lines 37-40), and "In concatenating ligands together using the methods and processes of the invention, two ligands that have mM (millimolar) affinities might be joined and yield a concatenated ligand that might have nM affinity (nanomolar) (column 14, line 66 to column 15, line 2). Griffey is full of expressions of desired outcomes and devoid of enablement. In particular here, Griffey gives no guidance on how to "concatenate" ligands to achieve greater binding affinity of linked ligand for target biomolecule. Griffey expresses only a wish, a speculation, such as "Two or more ligands can be joined by concatenation into new structural configurations to create a new ligand that will have improved binding characteristics or properties" (column 14, lines 51-53). The reader is uninformed as to: (1) how the ligands are joined, (2) what new structural configurations, and (3) what binding characteristics or properties these may be. Griffey further hopes that "Concatenation can be effected based on empirical or computational predictions" (column 14, lines 60-61). This may be so, but the reader will not learn how from Griffey. In contrast, the present invention does give definite teaching and examples of linking ligands, with examples of structural configurations, and measures their binding properties.

As the Examiner points out, certain ligands of the present invention (acetohydroxamic acid, 7B, 7A, 7C and 7E) are the same as those found in Hajduk. The applicant chose these ligands to compare the binding affinities as measured by NMR in Hajduk with mass spectrometry of the present invention, as well as other relative merits of NMR and mass spectrometry. Hajduk teaches only NMR detection of protein-ligand

binding. The stromelysin protein in Hajduk is ^{13}C and ^{15}N isotopically labelled (pages 5818, 5823), a significantly labor-intensive and distinguishing aspect. The protein targets of the present invention do not require isotope labelling. It is well known by the skilled chemist that while NMR and mass spectrometry are each important structure determination tools, they measure different properties, require different sample preparation procedures, and entail different data analysis to determine or infer structural information.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation to combine Griffey and Hajduk. There must also be a reasonable expectation of success in combining Griffey and Hajduk to practice the claimed invention. Applicants respectfully request withdrawal of the rejection under 35 USC § 103(a) of Griffey over Hajduk.

Rejection under 35 USC § 103(a)

Claims 27 and 29 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Griffey and Hajduk in view of Wells et al WO 00/00823, ("Wells").

The rejection is respectfully traversed. Claim 25 has been amended to include: (i) the step of identifying a 1:1 complex of linked ligand and target biomolecule by detecting the non-covalent binding of the linked ligand compound to the target biomolecule by mass spectrometry; (ii) members of the first and second set of ligands to having one or more functional groups selected from hydrogen bond donors, hydrogen bond acceptors, functional groups which form a cation at physiological pH, functional groups which form an anion at physiological pH, and functional groups which form hydrophobic interactions; and (iii) the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups. Neither Griffey nor Wells teach or suggest any one of elements (i), (ii) or (iii). The cited references thus collectively fail to teach or suggest all the elements of the claimed subject material.

Furthermore, Wells does not disclose or suggest detecting by mass spectrometry the non-covalent binding of a compound to a target where the compound is formed by chemically linking two ligands which bind to the target. Since Griffey does not disclose or suggest the first binding site is the same as the second binding site, and does not enable protein targets, there is no motivation, and the Examiner has not provided any showing of

a motivation, to combine these references to make obvious the claims of the present invention. There must also be a reasonable expectation of success in combining Griffey and Wells to practice the claimed invention. Applicants respectfully request withdrawal of the rejection under 35 USC § 103(a) of Griffey over Wells.

Rejection under 35 USC § 103(a)

Claims 31 and 32 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Griffey and in view of Ellman WO 99/49314, ("Ellman").

The rejection is respectfully traversed. Claim 25 has been amended to include: (i) the step of identifying a 1:1 complex of linked ligand and target biomolecule by detecting the non-covalent binding of the linked ligand compound to the target biomolecule by mass spectrometry; (ii) members of the first and second set of ligands to having one or more functional groups selected from hydrogen bond donors, hydrogen bond acceptors, functional groups which form a cation at physiological pH, functional groups which form an anion at physiological pH, and functional groups which form hydrophobic interactions; and (iii) the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups. Neither Griffey nor Ellman teach or suggest any one of elements (i), (ii) or (iii). Since all the claim limitations are not taught or suggested by the cited art, the *prima facie* case for obviousness is not established. Applicants respectfully request withdrawal of the rejection under 35 USC § 103(a) of Griffey over Ellman.

Rejection under 35 USC § 103(a)

Claims 31 and 33 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Griffey and Hajduk in view of Erlanson US 6919178, ("Erlanson").

The rejection is respectfully traversed. Claim 25 has been amended to include: (i) the step of identifying a 1:1 complex of linked ligand and target biomolecule by detecting the non-covalent binding of the linked ligand compound to the target biomolecule by mass spectrometry; (ii) members of the first and second set of ligands to having one or more functional groups selected from hydrogen bond donors, hydrogen bond acceptors, functional groups which form a cation at physiological pH, functional groups which form an anion at physiological pH, and functional groups which form hydrophobic

interactions; and (iii) the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups. Neither Griffey nor Erlanson teach or suggest any one of elements (i), (ii) or (iii). Since all the claim limitations are not taught or suggested by the cited art, the *prima facie* case for obviousness is not established. Applicants respectfully request withdrawal of the rejection under 35 USC § 103(a) of Griffey over Erlanson.

Conclusion

It is believed that the amendments made here place the application in condition for allowance and should be entered. With respect to any and all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter, and moreover have not acquiesced to any objection and/or rejection made by the Office. Applicants expressly reserve the right to pursue prosecution of any subject matter not presently claimed in one or more future or pending continuation and/or divisional applications.

In view of the above, reconsideration and allowance of this application are now believed to be in order. Applicants respectfully request that a timely Notice of Allowance be issued in this case. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at the number indicated below.

Respectfully submitted,
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